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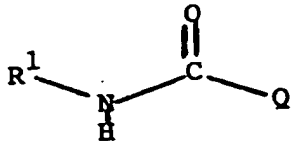
(54) New N-heteroarylamide derivatives as inhibitors of acyl coenzyme A: cholestrol acyl transferase.

(57) Compounds of the formula



the pharmaceutically acceptable salts thereof, wherein Q is a substituted pyridine or pyrimidine group and R^1 incorporates a hydrocarbon group of from 4 to 16 carbon atoms, are inhibitors of acyl coenzyme A: cholesterol acyltransferase (ACAT) and are useful as hypolipidemic and antiatherosclerosis agents.

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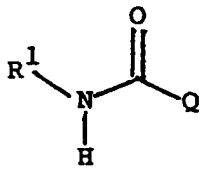
The present invention relates to new N-heteroarylamide derivatives, pharmaceutical compositions comprising such compounds, novel carboxylic acid and acid halide intermediates used in the synthesis of such compounds and the use of such compounds to inhibit intestinal absorption of cholesterol, lower serum cholesterol and reverse the development of atherosclerosis. The compounds are inhibitors of acyl coenzyme A: cholesterol acyltransferase (ACAT).

Cholesterol that is consumed in the diet (dietary cholesterol) is absorbed as free cholesterol by the mucosal cells of the small intestine. It is then esterified by the enzyme ACAT, packaged into particles known as chylomicrons, and released into the bloodstream. Chylomicrons are particles into which dietary cholesterol is packaged and transported in the bloodstream. By inhibiting the action of ACAT, the compounds of this invention prevent intestinal absorption of dietary cholesterol and thus lower serum cholesterol levels. They are therefore useful in preventing atherosclerosis, heart attacks and strokes.

By inhibiting the action of ACAT, the compounds of the present invention also enable cholesterol to be removed from the walls of blood vessels. This activity renders such compounds useful in slowing or reversing the development of atherosclerosis as well as in preventing heart attacks and strokes.

Other inhibitors of ACAT are referred to in United States Patents 4,716,175 and 4,743,605 (a divisional of the '175 patent) and in the European Patent Applications having publication numbers 0 242 610, 0 245 687 and 0 252 524. Certain ureas and thioureas as antiatherosclerosis agents are referred to in United States Patent 4,623,662.

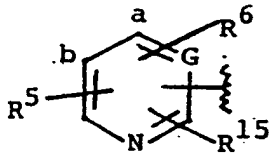
The present invention relates to compounds of the formula



I

wherein Q is $-CR^2R^3R^4$;

R^1 is



XXVI

R^2, R^3 and R^4 may be the same or different, and

(a) are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, A, XR^{10}, phenyl-(C_1-C_7) alkyl, and (C_5-C_6) cycloalkyl-(C_1-C_6) alkyl, with the proviso that at least one of R^2, R^3 and R^4 must be A, and with the proviso that when R^1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, either at least one of R^2, R^3 and R^4 must be XR^{10}, or two of R^2, R^3 and R^4 must be A; or

(b) R^2 and R^3 together with the carbon to which they are attached form a cyclic or bicyclic system selected from the group consisting of (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, (C_6-C_{14}) bicycloalkyl, (C_6-C_{14}) bicycloalkenyl, and aryl-fused and heteroaryl-fused systems containing 8 to 15 carbon atoms, one ring of any of said aryl-fused and heteroaryl-fused systems being aromatic and the ring containing the carbon to which R^2 and R^3 are attached being non-aromatic, one of the carbons of said aromatic ring being optionally replaced by sulfur or oxygen, one or more carbons of said non-aromatic ring being optionally replaced by sulfur or oxygen, and one or more carbons of said aromatic ring being optionally replaced by nitrogen; one or two carbons of said cycloalkyl or bicycloalkyl groups being optionally replaced by sulfur or oxygen, and said cyclic or bicyclic system being optionally substituted with one to five substituents independently selected from the group consisting of phenyl, substituted phenyl, (C_1-C_6) alkyl-and A, with the proviso that one and only one of said substituents is A, and one and only one of

said substituents is phenyl or substituted phenyl, said substituted phenyl being substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkylthio, halogen and trifluoromethyl; and R^4 is hydrogen, XR^{10} or A;

with the proviso that when R_1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, R^2 and R^3, together with the carbon to which they are attached, do not form a (C_3-C_7) cycloalkyl ring containing only carbon atoms:

A is a hydrocarbon containing 4 to 16 carbons and 0, 1 or 2 double bonds:

X is O, S, SO, SO_2, NH, $NR^{23}CO$ or NSO_2R^{24}, wherein R^{23} is hydrogen or (C_1-C_6) alkyl and R^{24} is (C_1-C_6) alkyl, phenyl or (C_1-C_3) alkyl-phenyl;

R^5, R^6 and R^{15} are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, (C_1-C_4)alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4)alkylthio, substituted phenylthio, heteroarylthio, heteroaryloxy, and $NR^{19}R^{20}$, wherein R^{19} and R^{20} are the same or different and are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, phenyl, substituted phenyl, (C_1-C_4) acyl, aroyl, and-substituted aroyl, wherein said substituted phenyl and substituted aroyl groups are substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, halogen and trifluoromethyl, or R^{19} and R^{20}, together with the nitrogen to which they are attached, form a piperidine or morpholine ring; and wherein R^5, R^6, R^{15} and R^{16}, when attached to a bicyclic system, may be attached to either ring of such system, with the proviso that no more than 3 non-hydrogen substituents may be attached to any one ring of such system:

R^{10} is selected from the group consisting of (C_4-C_{12}) cycloalkyl, (C_4-C_{12}) straight or branched alkyl, (C_4-C_{12}) cycloalkyl-(C_1-C_6) alkyl, phenyl- (C_1-C_6) alkyl, (substituted phenyl)-(C_1-C_6) alkyl, (C_1-C_6) alkyl-phenyl, (C_1-C_6) alkyl-(substituted phenyl), optionally substituted thiazoles, optionally substituted benzothiazoles, and optionally substituted pyridines; wherein the substituents on the substituted phenyl, substituted thiazoles, substituted benzothiazoles and substituted pyridines are selected from the group consisting of (C_1-C_4) alkoxy, (C_1-C_4) alkylthio, (C_1-C_6) alkyl, halo and trifluoromethyl:

G is selected from the group consisting of nitrogen and carbon,with the proviso that when G is nitrogen, the group XXVI is attached to the nitrogen of formula I at the 4 or 5 position of the pyrimidine ring (designated by a and b).

Examples of said aryl-fused and heteroaryl-fused systems are:

1,2,3,4-tetrahydronapthalene,
5,6,7,8,9-pentahydrobenzocycloheptene,
5,6,7,8,9,10-hexahydrobenzocyclooctene,
4,5,6-trihydro-1-thiapentalene,
4,5,6-trihydro-2-thiapentalene,
4,5,6,7-tetrahydrobenzo[b]thiophene,
4,5,6,7-tetrahydrobenzo[c]thiophene,
4,5,6-trihydro-1-oxapentalene,
4,5,6,7-tetrahydrobenzo[b]furan,
4,5,6-trihydro-1-azapentalene,
4,5,6,7-tetrahydrobenzo[b]pyrrole,
4,5,6-trihydro-1-oxa-3-azapentalene,
4,5,6,7-tetrahydrobenzo[d]oxazole,
4,5,6-trihydro-1-thia-3-azapentalene
4,5,6,7-tetrahydrobenzo[d]thiazole,
4,5,6-trihydro-1-oxa-2-azapentalene,
4,5,6,7-tetrahydrobenzo[d]oxazole,
4,5,6-trihydro-1-thia-2-azapentalene,
4,5,6,7-tetrahydrobenzo[d]thiazole,
4,5,6-trihydro-1,2-diazapentalene,
4,5,6,7-tetrahydrobenzo[d]pyrazole,
4,6-diazaindane and
5,6,7,8-tetrahydroquinazoline.

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, may be straight, branched or cyclic, and may include straight and cyclic moieties as well as branched and cyclic moieties.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "one or more carbons of said non-aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the non-aromatic ring of any of the aryl-fused or heteroaryl-fused systems described above, and not part of the aromatic ring of said aryl-fused system.

The term "one or more carbons of said aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the aromatic ring of any of the aryl-fused and heteroaryl-fused systems described above, or are part of both said aromatic and non-aromatic rings of said aryl-fused and heteroaryl-fused system.

The compounds of formula I may have optical centers and therefore may occur in different stereoisomeric configurations. The invention includes all stereoisomers of such compounds of formula I, including mixtures thereof

Preferred compounds of formula I are those wherein R^1 is 2-methyl-4,6-di(methylthio)- pyrimidin-5-yl, or 6-methyl-2,4-di(methylthio)- pyridin-3-yl. Other preferred compounds of formula I are those wherein:

R^2 is hexylthio, R^3 is octyl and R^4 is hydrogen; or

R^2 and R^3 together with the carbon to which they are attached form an indan-2-yl ring, and R^4 is 2-decyl; or

R^2 and R^3 together with the carbon to which they are attached form a 1,2,3,4-tetrahydronaphth-2-yl ring and R^4 is nonyl.

Specific preferred compounds of formula I are:
(2S)-N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
(2S)-N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2,2-dimethyldocecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2,2-dimethyldodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-4,5-dimethyl-trans-2-heptylcyclohex-4-ene-carboxamide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2-heptylnonanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]pentadecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl-]pentadecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-(Z)-9-octadecenoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-(Z)-9-octadecenoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-trans-3-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide;
N-[4,6-bis(methylthio)pyrimidin-5-yl]-trans-3-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide;
N-(2-methyl-4,6-dimethylthiopyrimidin-5-yl)-2-hexylthiodecanoicamide;
Other compounds of formula I are:
N-(4,6-dimethylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4,6-diethylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4-methoxy-6-ethylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4-ethoxy-6-methylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4-ethoxy-6-ethylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4-methoxy-6-ethoxyethylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(4-methoxy-6-butylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(2,4-dimethylthio-6-methylpyrimidin-5-yl)-2-heptylnonanoic amide;
N-(2-amino-4-methoxy-6-methylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-(2-acetamino-4-methoxy-6-methylthiopyrimidin-5-yl)-2-hexylthiodecanoic amide;
N-[4-methoxy-6-(2-furylmethylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-[4-methoxy-6-(2-propylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-(2-butylthio-4-methylpyridin-3-yl)-2-hexylthiodecanoic amide;
N-[2-(4-methoxyphenylthio)-4-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
N-[2-(2-furylmethylthio)-4-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
N-(2-ethylthio-4-methylpyridin-3-yl)-2-hexylthiodecanoic amide;
N-(2-ethylthio-4-methylpyridin-3-yl)-4,5-dimethyltrans-2-nonylcyclohex-4-enecarboxamide; and
N-(4,6-dimethylthiopyrimidin-5-yl)-2-decylindane-2-carboxamide.

The present invention also relates to a pharmaceutical composition for inhibiting ACAT, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in inhibiting ACAT, inhibiting

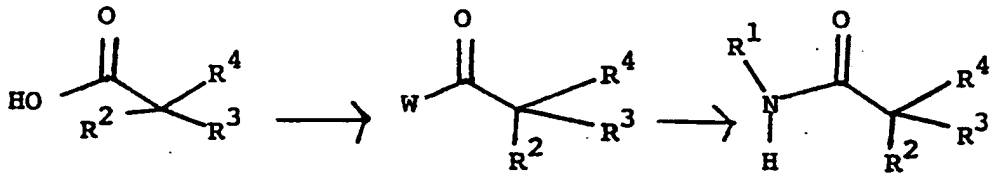
intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol, and a pharmaceutically acceptable carrier.

Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I salts are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicyclic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, di-p-toluoyl tartaric acid, and mandelic acid.

Reaction schemes 1-4 below illustrate the synthesis of the compounds of this invention. The compounds of formula I designated in the reaction schemes by the formulae IA, IB, IC, and ID, depending on the method by which they. prepared.

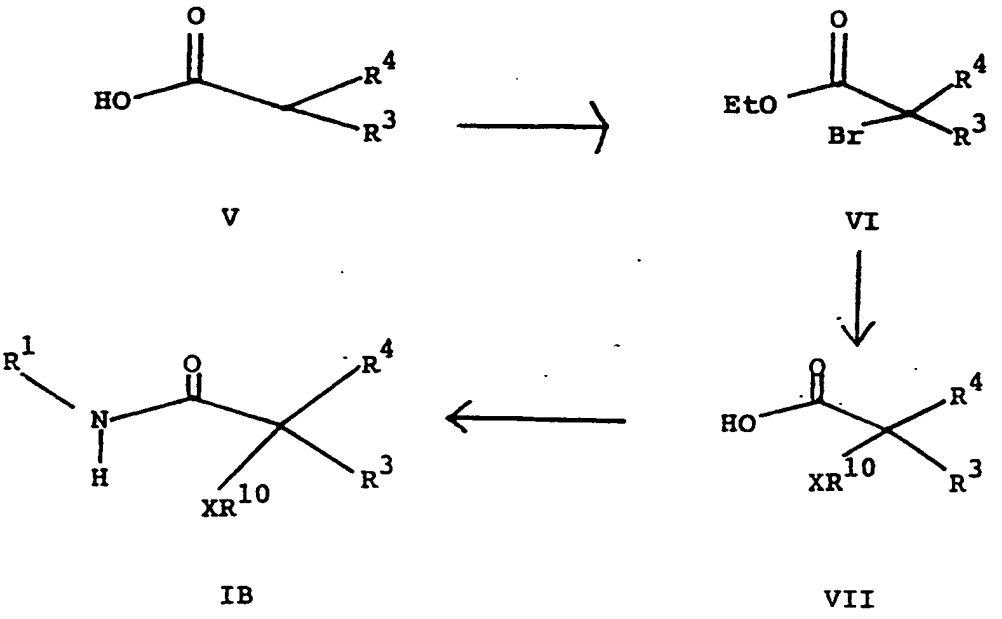
Except where otherwise stated, Q, R^1, R^2, R^3, R^4, R^5, R^6, R^{10}, R^{15}, p, X, A and G in the reaction schemes and discussion that follows are defined as above, and p is o, 1 or 2.

SCHEME 1



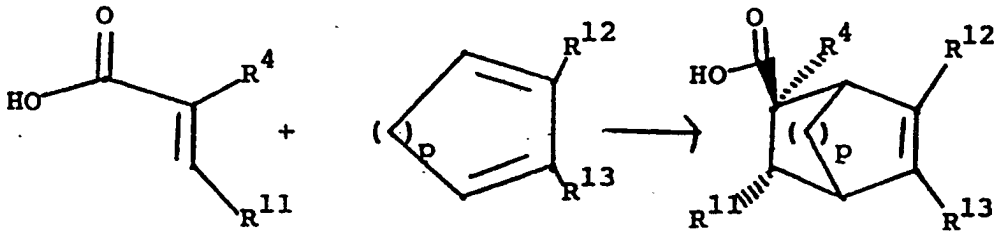
III IV IA

SCHEME 2

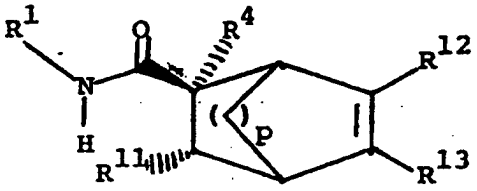


V VI IB VII

SCHEME 3

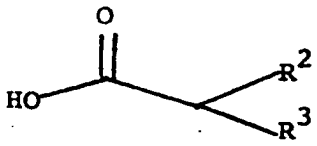


XIII IX X

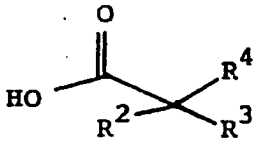


IC

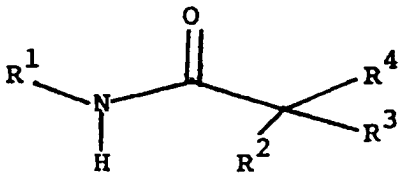
SCHEME 4



XI



XII



ID

Scheme 1 represents the synthesis of amides of the present invention having the formula IA, i.e., compounds of the formula I wherein Q is $-CR^2R^3R^4$, from the corresponding carboxylic acid having the formula III. An acid of formula III is first converted to the corresponding acid halide of formula IV, wherein W is chloro or bromo, by reacting it with a chlorinating or brominating agent. Examples of suitable chlorinating and brominating agents are oxalyl chloride, oxalyl bromide, thionyl chloride, thionyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, phosphorous

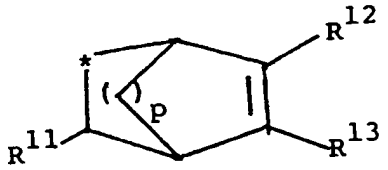
oxychloride, and phosphorous oxybromide. This reaction is typically carried out in the absence of a solvent or, alternatively, in the presence of a halogenated hydrocarbon solvent such as methylene chloride, for from about .5 to 48 hours (preferably from about 2 to 18 hours) at a temperature from about 0-250 °C (preferably at the reflux temperature of the reaction mixture). The acid halide so formed is then converted to the corresponding amide of the formula IA by reacting it with an amine of the formula R^1NH_2 and an acid scavenger such as dimethylaminopyridine, pyridine or triethylamine. This reaction is typically carried out in the absence of a solvent or in the presence of an inert solvent such as tetrahydrofuran or methylene chloride for from about 0.25 to 144 hours (preferably from about 2 to 72 hours) at a temperature from about -78 to 350 °C (preferably from about -20 to the reflux temperature of the reaction mixture).

Compounds of the formula I, wherein Q is $-CR^2R^3R^4$, R^2 is XR^{10}, one of R^3 and R^4 is hydrogen and the other is selected from hydrogen, (C_1-C_4) alkyl or A, i.e., compounds of the formula IB, may be prepared as illustrated in scheme 2. Referring to scheme 2, a carboxylic acid of the formula V, wherein one of R^3 and R^4 is hydrogen and the other is selected from hydrogen, (C_1-C_4) alkyl or A, is reacted for about 3 hours with thionyl chloride using no solvent, at the reflux temperature of the reaction mixture. Bromine and a catalytic amount of iodine are then added to the reaction mixture, and the resulting mixture is brought to reflux. After refluxing for about 18 hours, ethanol is added and the mixture is refluxed for about 1 more hour to produce a bromoester of the formula VI, wherein R^3 and R^4 are defined as they are for formula V above. The bromoester of formula VI is then converted to an ester having the same formula as formula VI except that the substituent -Br is replaced by the substituent $-XR^{10}$, (hereinafter referred to as formula VI'), by reacting it with a compound of the formula HXR^{10} and a base such as potassium carbonate or sodium hydride in an aprotic, polar solvent such as dimethylformamide, acetone or tetrahydrofuran, for about .5 to 48 hours (preferably from about 4 to 18 hours) at a temperature from -about -78 to 350 °C (preferably from about 0 °C to the reflux temperature of the reaction mixture). An acid of the formula VII, wherein R^3 and R^4 are defined as they are for formulas V and VI above, is then prepared by reacting the ester having formula VI' with a hydroxide such as sodium hydroxide. This reaction is typically carried out overnight in an lower alcohol solvent such as methanol or ethanol, at a temperature from about -78 to 350 °C (preferably from about 20 °C to the reflux temperature of the reaction mixture).

The acid of formula VII so prepared is then converted to an amide of the formula IB, wherein R^3 and R^4 are defined as they are for formulae V, VI and VII above, by the acid to amide synthesis illustrated in scheme 1 and described above.

Compounds of the formula IB, may be prepared, alternatively, by the following method. A compound of the formula V, as illustrated in scheme 2 and defined above, is reacted with thionyl chloride followed by bromine and a catalytic amount of iodine as described above, but quenching the reaction with water instead of ethanol, to form a compound of the formula $HOOCCBrR^3R^4$, wherein R^3 and R^4 are defined as they are for formula V. This compound is then converted, sequentially, to the corresponding acid chloride of the formula $ClCOCBrR^3R^4$ and the corresponding amide of the formula $R^1NHCOCBrR^3R^4$, wherein R^3 and R^4 are defined as they are for formula V, by the acid to amide synthesis illustrated in scheme 1 and described above. The amide of the formula $R^1NHCOCBrR^3R^4$ so formed is then reacted with a compound of the formula HXR^{10} and a base such as potassium carbonate and sodium hydride to form a compound having the formula IB, wherein R^3 and R^4 are defined as they are for formula V. This reaction is typically carried out in an aprotic, polar solvent such as dimethylformamide, acetone or tetrahydrofuran, for from about 0.5 to 48 hours (preferably from about 4 to 18 hours). The reaction may be carried out at temperatures ranging from about -78 to 350 °C (preferably from about 0 °C to the reflux temperature of the reaction mixture).

Scheme 3 illustrates the preparation of compounds of formula I, wherein Q is $CR^2R^3R^4$, R^4 is hydrogen or A, and R^2 and R^3, together with the carbon to which they are attached, form the bicyclic ring system



wherein the asterisk designates the carbon to which R^2 and R^3 are attached, and each of R^{12} and R^{13} are independently selected from the group consisting of hydrogen and (C_1-C_4) alkyl, or R^{12} and R^{13}, together with the carbons to which they are attached, form a benzene ring.

As illustrated in scheme 3, a Diels-Alder reaction is carried out between an acid of the formula XIII, wherein R^{11} is A, hydrogen, phenyl or substituted phenyl, and wherein R^{11} and the carboxyl group are trans to each other, and a diene of the formula IX, wherein R^{12} and R^{13} are as defined above. This reaction is typically carried out in a hydrocarbon solvent such as toluene, using a catalytic amount of an antioxidant such as hydroquinone. The reagents are generally reacted for about 1 to 10 days (preferably for about 3 to 5 days) in a sealed, high pressure apparatus at a temperature from about room temperature to 350 °C (preferably from about 100 to 150 °C). The reaction yields an acid of the formula X, which can be converted to the corresponding amide of the formula IC, wherein the carbons to which R^{12} and R^{13} are attached are bonded by a carbon-carbon double bond, by the acid to amide synthesis illustrated in scheme 1 and described above. The amide of formula IC so formed can be converted to an amide of the formula IC, wherein the carbons to which R^{12} and R^{13} are attached are bonded by a carbon-carbon single bond, by reacting it with a reducing agent such as hydrogen. Typically, the reduction is carried out using hydrogen gas in a high pressure apparatus, in an inert solvent such as acetic acid, and in the presence of a hydrogenation catalyst such as palladium on carbon.

The reduction maybe carried out at temperatures ranging from about -20 to 250 °C (preferably at room temperature). Fifty p.s.i. of hydrogen is the preferred pressure, through pressures greater than or equal to 1 atmosphere are suitable. The corresponding compound of formula IC, wherein the carboxyl group and R^{11} are cis to each other, may be prepared in a similar manner, but using the corresponding cis isomer of the acid of formula XIII.

When the procedure of scheme 3 described above is used to prepare a compound of formula IC wherein R^{12} and R^{13}, together with the carbon to which they are attached, form a benzene ring, the diene of formula IX is generally generated in situ in the presence of the acid of formula XIII or its ester by heating a mixture of 1,3-dihydrobenzo[c]thiophene 2,2-dioxide and such acid or ester. This reaction is typically carried out at a temperature of from about 235 to 300 °C (preferably from about 250 to 265 °C) under nitrogen for approximately from 0.5 to 24 hours (preferably for about 2 hours).

Scheme 4 illustrates the preparation of compounds of the formula I, wherein Q is $-CR^2R^3R^4$, R^4 is (C_1-C_4) alkyl or A, and R^2 and R^3 are each independently selected from the group consisting of hydrogen, (C_1-C_4) alkyl, A or XR^{10}; or R^2 and R^3, together with the carbon to which they are attached, form a cyclic or bicyclic system selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_{14}) bicycloalkyl, one or two carbons of said cycloalkyl and bicycloalkyl groups being optionally replaced with oxygen or sulfur; and aryl-fused and heteroaryl-fused systems containing 8 to 15 carbon atoms, one ring of any of said aryl-fused and heteroaryl-fused systems being aromatic and the ring containing the carbon to which R^2 and R^3 are attached being non-aromatic, one of the carbons of said aromatic ring being optionally replaced by sulfur or oxygen, one or more carbons of said non-aromatic ring being optionally replaced by sulfur or oxygen, and one or more carbons of said aromatic ring being optionally replaced by nitrogen. It also illustrates the preparation of compounds of the formula I, wherein Q is $-CR^2R^3R^4$, R^4 is XR^{10}, and R^2 and R^3, together with the carbon to which they are attached, form a cyclic or bicyclic system as defined immediately above. All compounds of the invention illustrated in scheme 4 are designated by the formula ID and are prepared by the following procedure.

An acid of the formula XI, wherein R^2 and R^3 are each independently selected from the group consisting of hydrogen, (C_1-C_4) alkyl, A or XR^{10}, or R^2 and R^3 together with the carbon to which they are attached, form a cyclic or bicyclic system as defined immediately above, is reacted with a base such as lithium diisopropylamide or hexamethyldisilazide, with or without an additive such as hexamethylphosphorous triamide, in a dry inert solvent such as tetrahydrofuran, and then reacted with a compound of the formula R^4Hal, wherein Hal is halogen and R^4 is (C_1-C_7) alkyl or A. The reaction is typically carried out at a temperature from about -78 to 40 °C (preferably from about -78 °C to room temperature) for about 0.5 to 48 hours (preferably for about 1.5 to 17 hours: 0.5 to 1 hour to generate the dianion of formula XI and 1 to 16 hours for the alkylation). The product of the reaction is an acid of the formula XII, wherein R^2 and R^3 are as defined immediately above, and R^4 is (C_1-C_7) alkyl or A. The acid of formula XII so formed may be converted to the corresponding amide of the formula ID, wherein R^2 and R^3 are as defined immediately above and R^4 is (C_1-C_7) alkyl or A, by the acid to amide synthesis illustrated in scheme 1 and described above.

Compounds of the formula ID, wherein R^4 is XR^{10}, are prepared by the same procedure as that described above for the preparation of compounds of the formula ID wherein R^4 is (C_1-C_7) alkyl or A, with one modification. The dianion of formula XI is reacted with a compound of formula $R^{10}SSR^{10}$ instead of $HalR^4$. This reaction produces an acid of the formula XII, wherein R^4 is XR^{10}. The acid of the formula XII so formed can then be converted to the corresponding amide of formula ID by the acid to amide synthesis illustrated in scheme 1 and described above.

The aminopyrimidine and aminopyridine intermediates used in the present invention are known in the literature or may be prepared by methods known in the art from intermediates that are known in the literature or commercially available. References for the preparation of many of the pyrimidine and pyridine intermediates can be found in the monographs "The Pyrimidines"; ed. by D.J. Brown (1962) and "Pyridine and its Derivatives", ed. by R.A. Abramovitch (1961), Interscience Publishers, Inc., New York, N.Y., and their supplements. The preparation of certain of these intermediates is described in greater detail below.

2,6-Disubstituted-5-amino-pyrimidine derivatives may be prepared by reacting the appropriately substituted 4,6-dihydroxypyrimidine with a nitrating agent such as fuming nitric acid in acetic acid at a temperature from about 15°C to about 40°C for a period of about 1 to about 5 hours. The resulting 5-nitropyrimidine is converted to the 2,4-dichloro-5-nitropyrimidine intermediate using a chlorinating agent such as phosphoryl chloride, alone or in the presence of a base, preferably diethylaniline, at a temperature from about 100 to about 115°C for a period of about 0.5 to about 2 hours. Procedures for carrying out these transformations are described in J. Chem. Soc., 3832 (1954).

The 2,6-bis(alkylthio)-5-nitropyrimidine derivatives may be prepared by reacting the appropriate dichloro intermediate with two equivalents of sodium alkylthiolate in a solvent such as dimethylformamide or, preferably, methanol, for about 4 to about 16 hours at a temperature from about 0 to about 30°C, preferably at ambient temperature. Monosubstitution of the dichloro intermediate is then accomplished by using one equivalent of nucleophile, at a reaction temperature of about 0 to about 100°C, depending on the reactivity of the nucleophile, in an inert solvent such as dimethylformamide or tetrahydrofuran, for a period of about 4 to about 16 hours.

The resulting monochloro derivative is then reacted with one equivalent of a different nucleophile to yield a disubstituted derivative with different substitutents on the carbon atoms at positions 2 and 4. The 2,6-disubstituted-5-nitropyrimidine is reduced using a reducing agent such as stannous chloride in concentrated hydrochloric acid or hydrogen gas with an appropriate catalyst, to yield the corresponding 5-aminopyrimidine derivative.

The novel pyridines of formula XXVIII and other 2,4-disubstituted-3-aminopyridine derivatives may be prepared by reacting the appropriate 2,4-dihydroxypyridine with a nitrating agent such as concentrated nitric acid at 80-100°C for 15-60 minutes. For example, the preparation of 2,4-dihydroxy-6-methyl-3-nitropyridine is described in J. Heterocyclic Chem., 1970, 7, 389. The resulting 2,4-dihydroxy-3-nitropyridine is sequentially converted to-the 2,4-dichloro-3-nitropyridine, 2,4-disubstituted-3-nitropyridine and 2,4-disubstituted-3-aminopyridine derivatives, using reaction conditions similar to those described above for the pyrimidine series.

Except where otherwise noted, pressure is not critical in any of the above reactions. Preferred temperatures for the above reactions were stated where known. In general, the preferred temperature for each reaction is the lowest temperature at which product will be formed. The preferred temperature for a particular reaction may be determined by monitoring the reaction using thin layer chromatography.

The novel compounds of formula I and the pharmaceutically acceptable salts thereof are useful as inhibitors of acyl coenzyme A: cholesterol acyltransferase (ACAT). As such they inhibit intestinal absorption of cholesterol in mammals and are useful in the treatment of high serum cholesterol in mammals, including humans. As used herein, treatment is meant to include both the prevention and alleviation of high serum cholesterol. The compound may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, parenterally and topically. In general, these compounds will be administered orally or parenterally at dosages between about 0.5 and about 30 mg/kg body weight of the subject to be treated per day, preferably from about .08 to 5 mg/kg. For an adult human of approximately 70 kg of body weight, the usual dosage would, therefore, be about 3.5 to about 2000 mg per day. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated and the activity of the compound being employed. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

A compound of formula I or a pharmaceutically acceptable salt thereof may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The resulting pharmaceutical compositions are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl

sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of a compound of formula I or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. Such solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitioneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The activity of the compounds of the present invention as ACAT inhibitors may be determined by a number of standard biological or pharmacological tests. For example, the following procedure was used to determine the ACAT inhibiting activity of compounds of formula I. ACAT was assayed in microsomes isolated from chow fed Sprague-Dawley rats according to Bilheimer, J.T., Meth. Enzymol., 111, ps 286-293 (1985), with minor modifications. Microsomes from rat liver were prepared by differential centrifugation and washed with assay buffer prior to use. The assay mixture contained 25 ul of BSA (40 mg/ml), 30 ul of rat liver microsome solution (100 ug microsomal protein), 20 ul of assay buffer (0.1 M K_2PO_4, 1.0 mM reduced Glutathione, pH 7.4), 20 ug of cholesterol in 100 ul of a 0.6% Triton WR-1339 solution in assay buffer, and 5 ul of test compound dissolved in 100% DMSO (total volume = 180 ul). The assay mixture was incubated for 30 min at 37°C. The reaction was started by the addition of 20 ul of 14C-Oleoyl-CoA (1000 uM, 2,000 dpm/nmol) and run for 15 min at 37°C. The reaction was stopped by the addition of 1 ml ETOH. The lipids were extracted into 4 ml hexane. A 3 ml aliquot was dried under N_2, and resuspended in 100 ul of chloroform. 50 ul of chloroform were spotted on a heat activated TLC plate and developed in hexane: diethyl ether: acetic acid (85:15:1, v:v:v). Incorporation of radioactivity into cholesteryl esters was quantified on a Berthold LB2842 Linear TIC Analyzer. ACAT inhibition was calculated relative to a DMSO control assay.

The activity of the compounds of formula I in inhibiting intestinal absorbtion of cholesterol may be determined by the procedure of Melchoir and Harwell, J. Lipid. Res., 26, 306-315 (1985).

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in deuterochoroform ($CDCl_3$) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; c, complex.

EXAMPLE 1

Ethyl 2-(4-n-Propylphenylthio)nonanoate

1.6 g (0.033 mole) sodium hydride (50% dispersion in mineral oil) was added to a solution of 5.0 g (0.033 mole) 4-propylthiophenol in 25 ml anhydrous dimethylformamide. After 15 minutes, 8.8 g (0.033 mole) ethyl 2-bromononanoate (prepared according to J. Labelled Compounds Radiopharm. 14, 713 (1978)) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was then diluted with 150 ml ethyl acetate and the resulting mixture was washed with 5 x 60 ml water and then with 60 ml saturated aqueous sodium chloride solution. The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting oil was chromatographed on 600 g silica gel, eluting with 7:3 hexane/methylene chloride to yield 9.0 g (81% yield) of the desired product as an oil.

^1H NMR($CDCl_3$): δ 0.88 (c,6H); 1.1-1.5 (c,total 12H) including 1.12 (t,3H); 1.54-1.93 (c,4H); 2.54 (t,2H); 3.56 (q,1H); 4.07 (q,2H); 7.1 (d,2H); 7.36 (d,2H).

EXAMPLE 1A

2-Hexylthiodecanoic Acid

17.3 g (0.36 mol) sodium hydride (50% dispersion in mineral oil) was added portionwise with stirring (gas evolution) to a solution of 26.8 ml. (0.19 mol) hexanethiol in 500 ml. anhydrous dimethylformamide.

The mixture was stirred at room temperature for 30 min., then 45.2g (0.18 mol) 2-bromodecanoic acid was added dropwise with stirring, keeping the temperature of the reaction mixture below 45°C. The reaction mixture was stirred at room temperature under nitrogen overnight. The mixture was then diluted with 500 ml. water and the pH of the resulting mixture was adjusted to 1.5 with 6N aqueous hydrochloric acid solution. This mixture was extracted with 3 x 400 ml. ethyl acetate and the combined ethyl acetate extracts were washed with 5 x 700 ml. water and 1 x 500 ml. brine. The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting oil was chromatographed on 2 kg. silica gel, eluting with methylene chloride to yield 35g (67% yield) of the desired product as an oil.

EXAMPLE 1B

Resolution of 2-hexylthiodecanoic acid

2-Hexylthiodecanoyl chloride was prepared by the procedure of Example 4A. A solution of 2-hexylthiodecanoyl chloride (2.39 g., 7.8 mmol) in 20 ml methylene chloride was added slowly with stirring under nitrogen to a solution of (R)-(-)-2-phenylglycinol (1.08 g, 7.9 mmol) and 4-dimethylaminopyridine (0.96 g, 7.9 mmol) in 80 ml methylene chloride at 5°C. The reaction mixture was stirred at room temperature overnight. Methylene chloride (100 ml.) was then added and the resulting solution was washed sequentially with 100 ml 1N aqueous hydrochloric acid solution, 100 ml water, 100 ml saturated aqueous sodium bicarbonate solution and 100 ml brine. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo to a solid residue (3.1 g). The diastereomers were separated by column chromatography on 800g silica gel using 1:1 hexane-diethyl ether as eluant. The less polar diastereomer (1.09 g, $[\alpha]_D^{RT}$ = -9.85° (CH_3OH); mp 98-100°C) and 0.99 g of the more polar diastereomer ($[\alpha]_D^{RT}$ = -9.46°(CH_3OH); mp 105-108°C) were obtained along with 0.36 g of a mixture of diastereomers (total yield 76%). A solution of the less polar diastereomer (900 mg, 2.2 mmol) in 42 ml 1,4-dioxane and 42 ml 6N aqueous sulfuric acid solution was heated at 105°C under nitrogen for 15 hours. The reaction mixture was cooled to room temperature, diluted with 80 ml water and the resulting mixture was extracted with 4 x 60 ml ethyl acetate. The combined ethyl acetate extracts were washed with 60 ml brine, dried over anhydrous sodium sulfate and concentrated in vacuo to yield (S)-(-)-2-hexylthiodecanoic acid as an oil (634 mg., 99.6% yield); $[\alpha]_D^{RT}$ = -59.5° (CH_3OH).

In a similar manner, hydrolysis of the more polar diastereomer yielded 98.4% of (R)-(+)-2-hexylthiodecanoic acid as an oil; $[\alpha]_D^{RT}$ = +54.0°(CH_3OH).

EXAMPLE 2

Ethyl 2-(4-t-Butylphenylthio)octanoate

A mixture of 5.0 g (0.02 mole) ethyl 2-bromooctanoate, 3.37 g (0.02 mole) p-t-butylthiophenol and 3.31 g (0.24 mole) potassium carbonate in 70 ml acetone was refluxed under nitrogen overnight. The reaction mixture was cooled to room temperature and filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on 500 g silica gel, eluting with 6:4 methylene chloride/hexane to yield 3.8 g (57% yield) of the desired product as an oil.

^1H NMR($CDCl_3$): δ 0.88 (c,3H); 1.1-1.52 (c,total 20H) including 1.14 (t,3H) and 1.3 (s); 1.66-2.11 (c,2H); 358 (q,1H); 4.1 (q,2H); 7.36 (m,4H).

EXAMPLE 3

2-(4-n-Propylphenylthio)nonanoic acid

A solution containing 5.7 (0.017 mole) of the title compound of Example 1, 35 ml of 1N aqueous sodium hydroxide solution (0.035 mole) and 3 ml methanol was refluxed overnight. The resulting solution was cooled to room temperature, acidified to pH 1.5 with 2N aqueous hydrochloric acid and extracted with 3 x 50 ml ethyl acetate. The combined ethyl acetate extracts were washed with 50 ml water and 50 ml saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo to yield the title compound as an oil (5.0 g, 96% yield) which was used in the subsequent reaction without further purification.

^1H NMR($CDCl_2$): δ 0.88 (c, 6H); 1.17-1.54 (c, 12H); 1.54-1.92 (c, 4H); 2.53 (t, 2H); 3.54 (t, 1H); 7.1 (d, 2H); 7.37 (d, 2H).

EXAMPLE 4 (ILLUSTRATIVE)

2-(4-n-Propylphenylthio)-N-(2,4,6-trimethoxyphenyl)nonanamide

1.54 g (5 mmole) of the title compound of Example 3 in 20 ml of thionyl chloride was refluxed for 3 hours and then concentrated to dryness in vacuo. 523 mg (1.6 mmole) of the resulting acid chloride was dissolved in 20 ml methylene chloride and to the solution was added 292 mg (1.6 mmole) 2,4,6-trimethoxyaniline and 195 mg (1.6 mmole) 4-dimethylaminopyridine. The resulting solution was stirred at room temperature overnight and then concentrated in vacuo. The residue was partitioned between 60 ml ethyl acetate and 20 ml 1N aqueous hydrochloric acid solution. The ethyl acetate layer was washed with 50 ml water and 50 ml saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was chromatographed on 100 g silica gel, eluting with 1:1 hexane/ethyl acetate to yield 370 mg (49% yield) of the title compound as a whitish solid.

EXAMPLE 4A

N-[2-methyl-4,6-bis(methylthio) pyrimidin-5-yl]-2-hexylthiodecanoic amide

A solution of 6.49 g (22.5 mmol) 2-hexylthiodecanoic acid in 40 ml thionyl chloride and 100 ml benzene was refluxed under nitrogen for 2.5 hours and then concentrated to dryness in vacuo. The resulting acid chloride (6.88 g, 22.5 mmol) was dissolved in 15 ml. methylene chloride and the solution was added dropwise to a solution of 4.63 g (23 mmol) 5-amino-4,6-bis(methylthio)-2-methylpyrimidine in 140 ml methylene chloride. The resulting solution was refluxed under nitrogen overnight. The reaction solution was then cooled, diluted with 140 ml methylene chloride and washed with 2 x 125 ml 3N aqueous hydrochloric acid solution, 1 x 125 ml water, 1 x 125 ml saturated aqueous sodium bicarbonate solution and 1 x 125 ml brine. The methylene chloride solution was dried over anhydrous sodium sulfate, filtered and concentrated to dryness in vacuo. The solid residue was recrystallized from diethyl ether yielding 5.35 g of the title compound, m.p. 99-101 °C. The filtrate was concentrated in vacuo and the residue was chromatographed on 400 g silica gel eluting with 9:1 hexane/ethyl acetate. Recrystallization of the product obtained by chromatography from diethyl ether yielded another 2.32 g of the title compound, m.p. 99°-101 °C (total yield 72.4%).

^{1}H NMR ($CDCl_3$): δ 0.87 (c, 6H); 1.21-1.84 (c, 21 H), 2.02 (m, 1H); 2.50 (s, 6H); 2.76 (s, 3H), 2.74 (t, 2H); 3.45 (t, 1H), 8.08 (s, 1H);

IR ($CHCl_3$): 2923, 2852, 1681, 1511, 1468, 1431, 1405 cm^{-1}.

EXAMPLE 4B

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide

A solution of 4.19 g (13.7 mmol) 2-hexylthiodecanoyl chloride, prepared according to Example 4A, in 15 ml methylene chloride was added dropwise with stirring under nitrogen to a solution of 2.75 g (13.7 mmol) 3-amino-2,4-bis(methylthio)-6-methylpyridine in 30 ml pyridine cooled to 5 °C. The reaction mixture was stirred at room temperature under nitrogen overnight. Methylene chloride (250 ml) was then added to the reaction mixture and the resulting solution was washed with 3 x 50 ml 3N aqueous hydrochloric acid solution, 2 x 50 ml water, 1 x 50 ml saturated aqueous sodium bicarbonate solution and 1 x 50 ml brine. The methylene chloride solution was dried over anhydrous sodium sulfate, filtered and concentrated to dryness in vacuo. The solid residue (6.5 g) was recrystallized from petroleum ether to yield 4.7 g of the title compound, m.p. 75-76.5 °C (72.8% yield).

^{1}H NMR ($CDCl_3$): δ 0.86 (c, 6H); 1.16-1.74 (c, 21H); 2.04 (m, 1H); 2.4 (s, 3H); 2.48 (s, 3H); 2.5 (s, 3H); 2.77 (t, 2H); 3.45 (t, 1H); 6.65 (s, 1H); 8.14 (s, 1H).

IR ($CHCl_3$): 2922, 2852, 1676, 1600, 1561, 1466 cm^{-1}.

EXAMPLE 5

2-Bromo-N-(2,4,6-trimethoxyphenyl)decanamide

2-Bromodecanoic acid (1 g, 3.8 mmol) was heated under reflux in thionyl chloride (10 ml) for 1 hour. The thionyl chloride was evaporated and the residue was dissolved in dry ether (10 ml) and added dropwise

to a solution of 2,4,6-trimethoxyaniline (0.7 g, 3.8 mmol) in pyridine (20 ml) at 0 °C and the mixture was stirred for 1.5 hours. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted three times with ethyl acetate (60 ml). The combined organics were extracted with water and brine and dried and concentrated. Recrystallization from isopropyl ether afforded 1.1 g (65%) of the title compound, m.p. 109-110 °C. This material was used directly in the next step.

EXAMPLE 6 (ILLUSTRATIVE EXAMPLE)

N-(2,4,6-Trimethoxyphenyl)-2-methyl-2-(4-(1-methylpropyl)phenoxy)nonanoic amide

By use of the procedures described in Examples 1 and 3, ethyl 2-bromononanoate and 4-(1-methylpropyl)-phenol were coupled and the product saponified to give 2-(4-(1-methylpropyl)phenoxy)-nonanoic acid. This material (1.0 g) was then methylated at the 2-position according to the procedure of Pfeffer, et. al. (J. Org. Chem., 1972, 37, 451) to give 2-methyl-2-hexanethiodecanoic acid (0.928 g). This material (0.86 g) was converted to the corresponding acid chloride with oxalyl chloride and coupled with 2,4,6-trimethoxyaniline (0.49 g) according to the procedure of Adams and Ulrich (J. Am. Chem. Soc., 1920, 42, 599) to give the title compound (1.12 g).

EXAMPLE 7 (ILLUSTRATIVE EXAMPLE)

N-(3-Methylquinolin-5-yl)-2-(4-(1-methylpropyl)-phenoxy)nonanoic amide

3-Methyl-4-chloro-5-nitroquinoline was hydrogenated using Pd/C to give 3-methyl-5-aminoquinoline. This material was coupled with 2-(4-(1-methylpropyl)phenoxy)nonanoic acid according to the procedure outlined in Example 6 to give the title compound.

EXAMPLE 8 (ILLUSTRATIVE EXAMPLE)

N-(6-Methoxyquinolin-5-yl)-2-(hexylthio)decanoic amide

Commercially available 6-methoxyquinoline (13.80 g) was nitrated according to the procedure of Campbell, et. al. (J. Am. Chem. Soc., 1946, 68, 1559) to give 5-nitro-6-methoxyquinoline (17.51 g). This crude product was directly reduced according to the procedure of Jacobs, et. al. (J. Am. Chem. Soc., 1920, 42, 2278) to give 5-amino-6-methoxyquinoline (6.25 g). This material (0.45 g) was coupled with 2-hexanethiodecanoic acid (0.75 g, prepared according to the procedures described in Examples 1 and 3) using the procedure described in Example 6 to give the title compound (0.63 g).

EXAMPLE 9 (ILLUSTRATIVE EXAMPLE)

N-(6-methylthioquinolin-5-yl)-2-(hexylthio)decanoic amide

Commercially available 6-chloroquinoline (33.3 g) was nitrated according to the procedure described in Example 33 to give 5-nitro-6-chloroquinoline (20.36 g). This material (15 g) was allowed to react with sodium methylthiolate according to the procedure of Massie (Iowa State Coll. J. Sci. 1946, 21, 41; CA 41:3044 g) to give 5-nitro-6-methylthioquinoline (13.61 g). This material (3.70 g) was reduced using iron (5.62 g) and hydrochloric acid (1.5 ml) in 50% aqueous ethanol (50 ml) to give 5-amino-6-methyl-thioquinoline (3.0 g). This material (3.0 g) was coupled with 2-hexanethiodecanoic acid (5.83 g, prepared according to the procedures described in Examples 1 and 3) using the procedure described in Example 6 , to give the title compound (3.8 g).

EXAMPLE 10

N-(3-Methoxypyridin-2-yl)-2-(4-(1-methylpropyl)-phenoxy)nonanoic amide

3-Methoxy-2-aminopyridine, prepared by reduction of the corresponding nitro compound according to Example 31, was coupled with 2-(4-(1-methylpropyl)-phenoxynonanoic acid according to Example 6 to give the title compound.

Oil. ^{1}H NMR: δ 8.90 (s, 1 H); 8.05 (d, 3 Hz, 1 H); 7.25 (m, 3 H); 6.97 (d, 3 Hz, 1 H); 6.89 (d, 9 Hz, 2 H); 4.64 (t, 7 Hz, 1 H); 3.74 (s, 3 H); 2.50 (tq, 12 & 12 Hz, 1 H); 1.98 (m, 2 H); 1.51 (m, 4 H); 1.18-1.08 (br, m, 11 H); 0.84 (t, 4 Hz, 3H); 0.76 (t, 5 Hz, 3 H). ^{13}C NMR: δ 172.40, 156.00, 140.10, 128.15, 119.86, 117.34, 115.45, 55.68, 40.84, 33.20, 32.30, 31.75, 31.24, 29.34, 29.11, 27.60, 25.26, 22.61, 21.70, 14.06, 12.19. IR ($CHCl_3$) cm^{-1}: 3387, 2922, 2854, 1702, 15.98. Mass spectrum m/e (relative intensity): M+ 412.34 (8), 313.22 (41), 263.22 (100), 151.08 (30). Anal.: Calc'd for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.80; N, 6.80. Found: C, 71.49, H, 8.88; N, 6.03.

EXAMPLE 11

N-(2-Methoxy-4-methylpyridin-2-yl)-2-(4-(1-methlypropyl)phenoxy)nonanoic amide

3-Nitro-4-methyl-2-pyridone was methylated with methyl iodide and reduced with zinc and acetic acid to give 2-methoxy-3-amino-4-methylpyridine. This material was coupled with 2-(4-(1-methylpropyl)-phenoxynonanoic acid according to the procedure of Example 6 to give the title compound.

Oil. ^{1}H NMR: δ 8.19 (s, 1 H); 7.10 (d, 7 Hz, 2 H); 7.04 (d, 5 Hz, 1 H); 6.93 (d, 7 Hz, 2 H); 6.03 (d, 5 Hz, 1 H); 4.63 (t, 6 Hz, 1 H); 3.48 (s, 3 H); 2.53 (tq, 11 & 11 Hz, 1 H); 2.07 (s, 3 H); 2.03 (m, 2 H); 1.55 (m, 4 H); 1.28 (m, 8 H); 1.18 (d, 6 Hz, 3 H); 0.87 (m, 3 H); 0.79 (t, 5 Hz, 3 H). ^{13}C NMR: δ 170.87, 159.58, 155.83, 143.55, 141.21, 133.70, 128.08, 124.35, 115.47, 109.06, 40.84, 37.44, 33.37, 31.75, 31.28, 31.25, 29.28, 29.07, 25.19, 22.61, 21.92, 19.47, 14.08, 12.20. IR ($CHCl_3$) cm^{-1}: 2920, 2852, 1685, 1655, 1606. Mass spectrum m/e (relative intensity): M+ 426.32 (10), 327.16 (7), 277.20 (52), 249.20 (35), 165.18 (100). Anal.: Calc'd for $C_{26}H_{38}N_2O_3$: C, 73.20; H, 8.98; N, 6.57. Found: C, 73.06; H, 9.11; N, 6.28.

EXAMPLE 12

N-(2-Methoxy-4-methylpyridin-2-yl)-2-(hexylthio)decanoic amide

3-Nitro-4-methyl-2-pyridone was methylated with methyl iodide and reduced with zinc and acetic acid to give 2-methoxy-3-amino-4-methylpyridine. This material was coupled with 2-hexylthiodecanoic acid according to the procedure of Example 6 to give the title compound.

M.p. 83-85 °C. ^{1}H NMR: δ 8.55 (s, 1 H); 7.04 (d, 6 Hz, 1 H); 6.07 (d, 6 Hz, 1 H); 3.54 (s, 3 H); 3.41 (t, 6 Hz, 1 H); 2.12 (s, 3 H); 2.03-1.17 (br, m, 22 H); 0.84 (t, 5 Hz, 3 H). ^{13}C NMR: δ 171.36, 159.74, 142.90, 133.40, 125.06, 109.20, 50.91, 37.47, 33.01, 31.82, 31.73, 31.38, 29.33, 29.27, 29.25, 28.52, 27.55 22.66, 22.52, 19.51, 14.10, 14.03. IR (KBr) cm^{-1}: 3232, 2920, 2850, 1652, 1592. Mass spectrum m/e (relative intensity): M+ 408.38 (5), 292.30 (16), 193.12 (17), 165.10 (54), 138.22 (100). Anal.: Calc'd for $C_{23}H_{40}N_2O_2S$: C, 67.60; H, 9.87; N, 6.86. Found: C, 67.56; H, 9.56; N, 6.58.

EXAMPLE 13

N-[2,4-bis(methylthio)pyridin-3-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 13.2% yield according to the procedure of Example 4A.

^{1}H NMR ($CDCl_3$) : δ 0.86 (c, 6H); 1.17-1.76(c, 21H), 2.03 (m, 1H), 2.42 (s, 3H); 2.51(s, 3H); 2.77 (t, 2H); 3.46 (t, 1H); 6.82 (d, 1H), 8.23 (s, 1H); 8.26 (d, 1H).

IR ($CHCl_3$): 2920, 2851, 1679, 1553, 1465 cm^{-1}.

EXAMPLE 14

N-[4,5-bis(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 7% yield according to the procedure of Example 4.

^{1}H NMR ($CDCl_3$) : δ 0.87 (c, 6H); 1.2-1.85 (c, 21 H); 2.02 (m, 1H); 2.52 (s, 6H); 2.74 (t, 2H); 3.45 (t, 1H); 8.18 (s, 1H); 8.65 (s, 1H).

IR ($CHCl_3$): 2923, 2852, 1681, 1521, 1466, 1406, 1357 cm^{-1}.

EXAMPLE 15

N-(4,6-dimethoxypyrimidin-5-yl)-2-hexylthiodecanoic amide

The title compound was prepared in 40% yield according to the procedure of Example 4.

^{1}H NMR ($CDCl_3$) : δ 0.88 (c, 6H); 1.22-2.0 (c, 22H); 2.64 (m, 1H); 3.43 (t, 1H); 3.97 (s, 6H); 7.90 (s, 1H); 8.33 (s, 1H).

IR ($CHCl_3$): 2922, 2852, 1680, 1582, 1491, 1465, 1410, 1399, 1312 cm^{-1}.

EXAMPLE 16

N-(4,6-diethoxypyrimidin-5-yl)-2-hexylthiodecanoic amide

The title compound was prepared in 76% yield according to the procedure of Example 4A.

^{1}H NMR ($CDCl_3$): δ 0.87 (c, 6H); 1.19-1.70 (c, 27H); 1.82 (m, 1H); 2.64 (m, 2H); 3.45 (t, 1H); 4.39 (q, 4H); 7.89 (s, 1H); 8.28 (s, 1H).

IR ($CHCl_3$): 2924, 2853, 1681, 1582, 1491, 1441, 1386, 1315 cm^{-1}.

EXAMPLE 17

N-[4-methoxy-6-(4-methoxyphenylthio)pyrimidin-5-yl]-2-hexyl- thiodecanoic amide

The title compound was prepared in 6% yield according to the procedure of Example 4A.

^{1}H NMR ($CDCl_3$) : δ 0.87 (m, 6H), 1.17-2.04 (c, 22H); 2.72 (t, 2H); 3.50 (t, 1H); 3.83 (s, 3H); 3.96 (s, 3H); 6.94 (d, 2H); 7.44 (d, 2H); 8.17 (s, 1H); 8.37 (s, 1H).

IR ($CHCl_3$): 2900, 2840, 1700, 1600, 1565, 1480.

EXAMPLE 18

N-[4,6-bis(ethylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 8% yield according to the procedure of Example 4B.

^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.17-2.06 (c, 28H); 2.62 (m, 4H); 2.75 (t, 2H); 3.45 (t, 1H); 8.15 (s, 1H); 8.61 (s, 1H).

IR ($CHCl_3$): 2922, 2852, 1706, 1520, 1466, 1405, 1355 cm^{-1}.

EXAMPLE 19

N-[4-methoxy-6-(2-ethoxyethylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 38% yield according to the procedure of Example 4A.

^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.16-1.85 (c) and 1.19 (t) (total 24H); 1.94 (m, 1H); 2.68 (t, 2H); 3.32-3.57 (c), 3.52 (q) (total 5H); 3.65 (t, 2H), 3.95 (s, 3H); 8.03 (s, 1H); 8.47 (s, 1H).

IR ($CHCl_3$): 2952, 2925, 2854, 1684, 1562, 1541, 1481, 1408, 1385 cm^{-1}.

EXAMPLE 20

N-[2-(4-pyridinylthio)-4-methylpyridin-3-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 10% yield according to the procedure of Example 4.

^{1}H NMR ($CDCl_3$): δ 0.86 (m, 6H); 1.17-1.84 (c, 21H); 1.95 (m, 1H); 2.30 (s, 3H); 2.62 (t, 2H); 3.4 (t, 1H); 7.17 (d, 1H); 7.27 (m, 2H); 8.31 (d, 1H); 8.48 (b, 2H); 8.55 (s, 1H).

IR ($CHCl_3$): 2921, 2851, 1680, 1574, 1471 cm^{-1}.

EXAMPLE 21

N-[4-methoxy-6-(1-methyl-5-tetrazolylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 43% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.18-1.87 (c, 21H); 1.98 (m, 1H); 2.65 (t, 2H); 3.49 (t, 1H); 4.02 (s, 3H); 4.12 (s, 3H); 8.26 (s, 1H); 8.58 (s, 1H).
IR ($CHCl_3$): 2900, 2840, 1690, 1560, 1485 cm^{-1}.

EXAMPLE 22

N-[2-(2-furylmethylthio)-4-methylpyridin-3-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 10% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.17-2.03 (c, 22H); 2.19 (s, 3H), 2.65 (m, 2H); 3.42 (t, 1H); 4.47 (s, 2H); 6.24 (m, 2H); 6.92 (d, 1H); 7.30 (d, 1H); 8.18 (s, 1H); 8.25 (d, 1H).
IR ($CHCl_3$): 2920, 2850, 1706, 1675, 1481 cm^{-1}.

EXAMPLE 23

N-[2,4,6-tris(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 79% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (c, 6H); 1.17-1.86 (c, 21H); 2.01 (m, 1H); 2.50 (s, 6H); 2.56 (s, 3H); 2.73 (t, 2H); 3.43 (t, 1H); 8.06 (s, 1H).
IR ($CHCl_3$): 2922, 2852, 1686, 1499, 1465, 1347 cm^{-1}.

EXAMPLE 24

N-(2,4,6-trimethoxypyrimidin-5-yl)-2-hexylthiodecanoic amide

The title compound was prepared in 74% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.18-2.0 (C, 22H); 2.63 (m, 2H); 3.42 (t, 1H); 3.93 (s, 6H); 3.95 (s, 3H); 7.71 (s, 1H).
IR ($CHCl_3$): 2923, 2851, 1675, 1607, 1582, 1482, 1467, 1398, 1379 cm^{-1}.

EXAMPLE 25

N-[2-methyl-4,6-bis(ethylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 52% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.19-1.84 (c, 27H); 2.0 (m, 1H); 2.57 (s, 3H); 2.75 (t, 2H); 3.15 (q, 4H); 3.44 (t, 1H); 8.04 (s, 1H).
IR ($CHCl_3$): 2920, 2852, 1680, 1467, 1406, 1359, 1314 cm^{-1}.

EXAMPLE 26

N-(4,6-dimethoxypyrimidin-5-yl)-2-heptylnonanoic amide

The title compound was prepared in 53% yield according to the procedure of Example 4.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.18-1.8 (c, 24H); 2.24 (m, 1H); 3.97 (s, 6H); 8.32 (s, 1H).
IR ($CHCl_3$): 2921, 2851, 1686, 1583, 1487, 1463, 1408, 1400, 1312, 1121 cm^{-1}.

EXAMPLE 27

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-heptylnonanoic amide

The title compound was prepared in 48% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.17-1.82 (c, 24H); 2.28 (m, 1H); 2.4 (s, 3H); 2.48 (s, 3H); 2.50 (s, 3H); 6.53 (s, 1H); 6.63 (s, 1H).
IR ($CHCl_3$): 2921, 2851, 1686, 1560, 1460, 1338 cm^{-1}.

EXAMPLE 28

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-heptylnonanoic amide

The title compound was prepared in 35% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 6H); 1.18-1.8 (c, 24H); 2.27 (m, 1H); 2.49 (s, 6H); 2.59 (s, 3H); 6.46 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1691, 1505, 1462, 1431, 1406, 1360, 1300 cm^{-1}.

EXAMPLE 29

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2,2-dimethyldodecanoic amide

The title compound was prepared in 49% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.67 (c) and 1.32 (s) (total 24H); 2.39 (s, 3H); 2.48 (s, 3H); 2.50 (s, 3H); 6.63 (s, 1H); 6.72 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1678, 1559, 1459, 1338 cm^{-1}.

EXAMPLE 30

N-[2,4-bis(methylthio)pyridin-3-yl]-2,2-dimethyldodecanoic amide

The title compound was prepared in 40% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.68 (c) and 1.33 (s)(total 24H); 2.41 (s, 3H); 2.51 (s, 3H); 6.79 (s, 1H); 6.82 (d, 1H); 8.25 (d, 1H).
IR ($CHCl_3$): 2920, 2850, 1679, 1553, 1462, 1370 cm^{-1}.

EXAMPLE 31

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2,2-dimethyldodecanoic amide

The title compound was prepared in 23% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.2-1.68 (c) and 1.31 (s)(total 24H); 2.49 (s, 6H); 2.59 (s, 3H); 6.65 (s, 1H).
IR ($CHCl_3$): 2923, 2849, 1683, 1510, 1467, 1407, 1362, 1301 cm^{-1}.

EXAMPLE 32

N-[4,6-bis(methylthio)pyrimidin-5-yl]-2,2-dimethyldodecanoic amide

The title compound was prepared in 43% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.2-1.68 (c) and 1.32 (s)(total 24H); 2.51 (s, 6H); 6.74 (s, 1H); 8.64 (s, 1H).
IR ($CHCl_3$): 2924, 2851, 1688, 1522, 1468, 1406, 1359 cm^{-1}.

EXAMPLE 33

N-[2,4-bis(ethylthio)-6-methylpyridin-3-yl]-tetradecanoic amide

The title compound was prepared in 68% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.19-1.62 (c, 26H); 1.76 (m, 2H); 2.39 (t, 2H); 2.46 (s, 3H); 2.91 (q, 2H); 3.15 (q, 2H); 6.52 (s, 1H), 6.68 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1687, 1556, 1460 cm^{-1}.

EXAMPLE 34

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-tetradecanoic amide

The title compound was prepared in 59% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.82 (c, 22H); 2.40 (s), 2.48 (s), 2.50 (s) and 2.37-2.6 (m)(total 11H); 6.50 (s, 1H); 6.64 (s, 1H).
IR ($CHCl_3$): 2917, 2847, 1693, 1570, 1472 cm^{-1}.

EXAMPLE 35

N-[4,6-bis(methylthio)pyrimidin-5-yl]-tetradecanoic amide

The title compound was prepared in 76% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.62 (c, 20H); 1.76 (m, 2H); 2.41 (t, 2H); 2.52 (s, 6H); 6.51 (s, 1H); 8.65 (s, 1H).
IR ($CHCl_3$): 2917, 2847, 1690, 1511, 1459, 1405, 1355 cm^{-1}.

EXAMPLE 36

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]tetradecanoic amide

The title compound was prepared in 78% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.19-1.61 (c, 20H); 1.75 (m, 2H); 2.40 (t, 2H); 2.49 (s, 6H); 2.59 (s, 3H); 6.45 (s, 1H).
IR ($CHCl_3$): 2917, 2847, 1689, 1460, 1406, 1357 cm^{-1}.

EXAMPLE 37

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]pentadecanoic amide

The title compound was prepared in 53% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.81 (c, 24H), 2.4 (t, 2H); 2.5 (s, 6H), 2.6 (s, 3H); 6.44 (s, 1H).
IR ($CHCl_3$): 2918, 2847, 1689, 1460, 1425, 1405 cm^{-1}.

EXAMPLE 38

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]pentadecanoic amide

The title compound was prepared in 68% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.82 (c, 24H); 2.40 (s + t, 5H); 2.51 (s, 3H); 6.52 (s, 1H); 6.63 (s, 1H).
IR ($CHCl_3$): 2921, 2849, 1686, 1612, 1559, 1459 cm^{-1}.

EXAMPLE 39

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]hexadecanoic amide

The title compound was prepared in 78.2% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.49 (c, 22H), 1.57 (m, 2H); 1.75 (m, 2H); 2.39 (t, 2H); 2.49 (s, 6H); 2.59 (s, 3H); 6.46 (s, 1H).
IR ($CHCl_3$): 2919, 2849, 1688, 1459, 1406, 1358 cm^{-1}.

EXAMPLE 40

N-[4,6-bis(ethylthio)pyrimidin-5-yl]hexadecanoic amide

The title compound was prepared in 70% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.5 (c, 28H); 1.58 (m, 2H); 1.76 (m, 2H); 2.4 (t, 2H); 3.15 (q, 4H); 6.49 (s, 1H); 8.61 (s, 1H).
IR ($CHCl_3$): 2918, 2848, 1692, 1460, 1404, 1356 cm^{-1}.

EXAMPLE 41

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]hexadecanoic amide

The title compound was prepared in 8.6% yield according to the procedure of Example 4.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.84 (c, 26H); 2.39 (s + t, 5H); 2.48 (s, 3H); 2.5 (s, 3H); 6.5 (s, 1H); 6.64 (s, 1H).
IR ($CHCl_3$): 2921, 2849, 1690, 1612, 1560, 1460 cm^{-1}.

EXAMPLE 42

N-[4,6-bis (methylthio)pyrimidin-5-yl]hexadecanoic amide

The title compound was prepared in 58.8% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.49 (c, 22H); 1.57 (m, 2H); 1.76 (m, 2H); 2.41 (t, 2H); 2.51 (s, 6H); 6.54 (s, 1H); 8.65 (s, 1H).
IR ($CHCl_3$): 2920, 2849, 1696, 1521, 1465, 1407, 1358

EXAMPLE 43

N-[4,6-bis(methylthio)pyrimidin-5-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 61% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.17-1.5 (c, 18H); 1.59 (m, 2H); 1.76 (m, 2H); 2.0 (c, 4H); 2.41 (t, 2H); 2.51 (s, 6H); 5.34 (m, 2H); 6.56 (s, 1H); 8.65 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1693, 1515, 1465, 1407, 1358 cm^{-1}.

EXAMPLE 44

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 55% yield according to the procedure of Example 4.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.68 (c, 20H); 1.77 (m, 2H); 2.0 (c, 4H); 2.39 (s + t, 5H); 2.47 (s, 3H); 2.49 (s, 3H); 5.34 (m, 2H); 6.51 (s, 1H); 6.63 (s, 1H).
IR ($CHCl_3$): 2918, 2850, 1686, 1560, 1460, 1339 cm^{-1}.

EXAMPLE 45

N-[4,6-bis(ethylthio)pyrimidin-5-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 52.3% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.19-1.5 (c, 24H); 1.58 (m, 2H); 1.76 (m, 2H); 2.01 (c, 4H); 2.40 (t, 2H); 3.15 (q, 4H); 5.34 (m, 2H); 6.5 (s, 1H); 8.61 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1691, 1508, 1460, 1405, 1355 cm^{-1}.

EXAMPLE 46

N-[2-methyl-4,6-bis(ethylthio)pyrimidin-5-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 66.7% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.5 (c, 24H); 1.58 (m, 2H); 1.75 (m, 2H); 2.01 (c, 4H); 2.38 (t, 2H); 2.57 (s, 3H), 3.14 (q, 4H); 5.34 (m, 2H); 6.41 (s, 1H).
IR ($CHCl_3$): 2919, 2849, 1690, 1459, 1407, 1357, 1312 cm^{-1}.

EXAMPLE 47

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 55% yield according to the procedure of Example 4.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.48 (c, 18H); 1.58 (m, 2H); 1.76 (m, 2H); 2.0 (c, 4H); 2.39 (t, 2H); 2.49 (s, 6H); 2.59 (s, 3H); 5.33 (m, 2H); 6.46 (s, 1H).
IR ($CHCl_3$): 2923, 2850, 1692, 1508, 1464, 1429, 1406, 1360 cm^{-1}.

EXAMPLE 48

N-[2,4-bis(methylthio)pyridin-3-yl]-(Z)-9-octadecenoic amide

The title compound was prepared in 43% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.18-1.5 (c, 18H); 1.59 (m, 2H); 1.77 (m, 2H); 2.01 (c, 4H); 2.41 (s + t, 5H); 2.51 (s, 3H); 5.34 (m, 2H), 6.57 (s, 1H); 6.82 (d, 1H); 8.25 (d, 1H).
IR ($CHCl_3$): 2920, 2850, 1687, 1552, 1461, 1375 cm^{-1}.

EXAMPLE 49

N-[4,6-bis(methylthio)pyrimidin-5-yl]-2-dodecylthioacetamide

The title compound was prepared in 61% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.22-1.49 (c, 18H); 1.67 (m, 2H); 2.53 (s, 6H); 2.74 (t, 2H); 3.41 (s, 2H); 8.3 (s, 1H); 8.67 (s, 1H).
IR ($CHCl_3$): 2917, 2847, 1688, 1467, 1405, 1355 cm^{-1}.

EXAMPLE 50

N-[4,6-bis(ethylthio)pyrimidin-5-yl]-2-dodecylthioacetamide

The title compound was prepared in 52% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.22-1.5 (c, 24H); 1.67 (m, 2H); 2.74 (t, 2H); 3.17 (q, 4H); 3.41 (s, 2H); 8.27 (s, 1H); 8.63 (s, 1H).
IR ($CHCl_3$): 2918, 2848, 1687, 1466, 1404, 1353 cm^{-1}.

EXAMPLE 51

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-dodecylthioacetamide

The title compound was prepared in 45% yield according to the procedure of Example 4.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.46 (c, 18H); 1.67 (m, 2H); 2.41 (s, 3H); 2.49 (s, 3H); 2.51 (s, 3H); 2.76 (t, 2H); 3.41 (s, 2H); 6.66 (s, 1H); 8.25 (s, 1H).
IR($CHCl_3$): 2918, 2848, 1678, 1561, 1476, 1337 cm^{-1}.

EXAMPLE 52

N-[2,4-bis(methylthio)pyridin-3-yl]-2-dodecylthioacetamide

The title compound was prepared in 24% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.17-1.48 (c, 18H); 1.67 (m, 2H); 2.43 (s, 3H); 2.53 (s, 3H); 2.76 (t, 2H); 3.42 (s, 2H); 6.85 (d, 1H); 8.28 (d, 1H); 8.34 (s, 1H).
IR ($CHCl_3$): 2919, 2849, 1683, 1553, 1475, 1432, 1376 cm^{-1}.

EXAMPLE 53

N-[2,4-bis(ethylthio)-6-methylpyridin-3-yl]-2-dodecylthioacetamide

The title compound was prepared in 37% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.47 (c, 24H); 1.67 (m, 2H); 2.47 (s, 3H); 2.77 (t, 2H); 2.92 (q, 2H); 3.15 (q, 2H); 3.41 (s, 2H); 6.69 (s, 1H); 8.24 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1680, 1559, 1474, 1337 cm^{-1}.

EXAMPLE 54

N-[2,4-bis(ethylthio)pyridin-3-yl]-2-dodecylthioacetamide

The title compound was prepared in 27% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.18-1.47 (c, 24H); 1.67 (m, 2H); 2.77 (t, 2H); 2.95 (q, 2H); 3.18 (q, 2H); 3.42 (s, 2H); 6.88 (d, 1H); 8.25 (d, 1H); 8.34 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1682, 1551, 1474, 1375 cm^{-1}.

EXAMPLE 55

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-trans-3-nonyl1,2,3,4-tetrahydro-2-naphthoic amide

The title compound was prepared in 7% yield according to the procedure of Example 4A. ^{1}H NMR ($CDCl_3$): δ 0.87 (m, 3H); 1.2-1.72 (c, 16H); 2.16 (m, 1H); 2.41-2.64 (c), 2.51 (s), 2.60 (s)(total 11H); 2.94-3.28 (c, 3H); 6.54 (s, 1H); 7.12 (c, 4H).
IR ($CHCl_3$): 2900, 2830, 1690, 1460 cm^{-1}.

EXAMPLE 56

N-[4,6-bis(methylthio)pyrimidin-5-yl]-3-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide

The title compound was prepared in 8% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (m, 3H); 1.18-1.75 (c, 16H); 2.17 (m, 1H); 2.4-2.62, (c), 2.53 (s)(total 8H); 2.93-3.27 (c, 3H); 6.6 (s, 1H); 7.13 (c, 4H); 8.66 (s, 1H).
IR ($CHCl_3$): 2900, 2830, 1700, 1610, 1470 cm^{-1}.

EXAMPLE 57

N-[4,6-bis(methylthio)pyrimidin-5-yl]-2-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide

The title compound was prepared in 11% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.18-1.67 (c, 15H); 1.91 (m, 2H); 2.24 (m, 1H); 2.45 (s, 6H); 2.78-2.96 (c, 2H); 3.07 (m, 1H); 3.28 (d, 1H); 6.74 (s, 1H); 7.13 (s, 4H); 8.60 (s, 1H).
IR ($CHCl_3$): 2921, 2849, 1681, 1518, 1454, 1406, 1357 cm^{-1}.

EXAMPLE 58

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-decylcyclopentanecarboxamide

The title compound was prepared in 27.4% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.82 (c, 24H); 2.27 (m, 2H); 2.49 (s, 6H); 2.59 (s, 3H); 6.6 (s, 1H).
IR ($CHCl_3$): 2921, 2851, 1681, 1450, 1407, 1360 cm^{-1}.

EXAMPLE 59

N-[4,6-bis(methylthio)pyrimidin-5-yl]-2-decylcyclopentanecarboxamide

The title compound was prepared in 20% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.21-1.82 (c, 24H); 2.28 (m, 2H); 2.51 (s, 6H); 6.69 (s, 1H); 8.64 (s, 1H).
IR ($CHCl_3$): 2922, 2850, 1682, 1452, 1405, 1358 cm^{-1}.

EXAMPLE 60

N-[4,6-bis(methylthio)pyrimidin-5-yl]-2-decylindane-2-carboxamide

The title compound was prepared in 33.7% yield acording to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H); 1.14-1.88 (d, 18H); 2.49 (s, 6H); 3.04 (d, 2H); 3.58 (d, 2H); 6.63 (s, 1H); 7.2 (c, 4H); 8.63 (s, 1H).
IR ($CHCl_3$): 2922, 2850, 1687, 1526, 1458, 1407, 1359 cm^{-1}.

EXAMPLE 61

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-methylthiotetradecanoic amide

The title compound was prepared in 66% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.87 (c, 21H); 2.03 (m, 1H); 2.31 (s, 3H); 2.41 (s, 3H); 2.50 (s, 3H); 2.53 (s, 3H), 3.38 (t, 1H); 6.66 (s, 1H); 8.05 (s, 1H).
IR ($CHCl_3$): 2919, 2850, 1677, 1559, 1522, 1468, 1438 cm^{-1}.

EXAMPLE 62

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-methylthiotetradecanoic amide

The title compound was prepared in 79% yield according to the procedure of Example 4A.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.21-1.86 (c, 21H); 2.04 (m, 1H), 2.29 (s, 3H); 2.52 (s, 6H); 2.62 (s, 3H); 3.37 (t, 1H); 8.0 (s, 1H).
IR ($CHCl_3$): 2918, 2849, 1681, 1465, 1405 cm^{-1}.

EXAMPLE 63

N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-ethylthiotetradecanoic amide

The title compound was prepared in 51% yield according to the procedure of Example 4B.
^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.7 (c, 23H); 1.8 (m, 1H); 2.06 (m, 1H); 2.41 (s, 3H); 2.50 (s, 3H);

2.53 (s, 3H); 2.8 (q, 2H); 3.48 (t, 1H); 6.66 (s, 1H); 8.13 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1675, 1560, 1466 cm^{-1}.

EXAMPLE 64

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-ethylthiotetradecanoic amide

The title compound was prepared in 51% yield according to the procedure of Example 4A.
^1H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.2-1.88 (c, 24H); 2.03 (m, 1H); 2.52 (s, 6H); 2.62 (s, 3H); 2.79 (q, 2H); 3.48 (t, 1H); 8.08 (s, 1H).
IR ($CHCl_3$): 2920, 2850, 1679, 1465, 1405 cm^{-1}.

EXAMPLE 65

N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-4,5-dimethyl-trans-2-heptylcyclohex-4-enecarboxamide

The title compound was prepared in 31% yield according to the procedure of Example 4A.
^1H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.16-2.48 (c, 24H); 2.5 (s, 6H); 2.59 (s, 3H); 6.56 (s, 1H).
IR ($CHCl_3$): 2918, 2850, 1687, 1458, 1406, 1360 cm^{-1}.

EXAMPLE 66

N-[4,6-bis(methylthio)pyrimidin-5-yl]-4,5-dimethyl-trans-2-heptylcyclohex-4-enecarboxamide

The title compound was prepared in 27% yield according to the procedure of Example 4A.
^1H NMR ($CDCl_3$): δ 0.87 (t, 3H); 1.17-2.49 (c, 24H); 2.52 (s, 6H); 6.64 (s, 1H); 8.65 (s, 1H).
IR ($CHCl_3$): 2920, 2852, 1690, 1458, 1405, 1356 cm^{-1}.

EXAMPLE 67

3-Amino-2,4-bis(methylthio)-6-methylpyridine

To a solution of 15.5 g (0.22 mol) sodium methanethiolate in 200 ml methanol was added slowly with stirring under nitrogen a solution of 20.8 g (0.1 mol) 3-nitro-2,4-dichloro-6-methylpyridine in 150 ml methanol. A precipitate formed and the mixture was stirred overnight at room temperature. The mixture was then filtered and the solid was washed first with methanol and then with water. 3-Nitro-2,4-bis(methylthio)-6-methylpyridine (18.9 g, 82% yield) was obtained as a yellow solid, mp 172-176 °C.
^1H NMR ($CDCl_3$): δ 2.45 (s, 3H); 2.51 (s, 3H); 2.55 (s, 3H); 6.77 (s, 1H).
A mixture of 18.9 g (0.082 mol) 3-nitro-2,4-bis(methylthio)-6-methylpyridine and 18.9 g Raney nickel in 600 ml. 1,4-dioxane and 300 ml methanol was shaken with hydrogen (15 psi) in a Parr hydrogenation apparatus for 3.5 hr. The catalyst was filtered and the filtrate was concentrated to dryness in vacuo. The solid residue was chromatographed on silica-gel (650g), eluting with 9:1 hexane/ethyl acetate to yield 14.0g. (85% yield) of the title compound as an off-white solid.
NMR ($CDCl_3$): δ 2.42 (s, 3H); 2.44 (s, 3H); 2.59 (s, 3H); 4.02 (b, 2H); 6.72 (s, 1H).
The title compounds of Examples 68-70 were prepared according to the procedure of Example 67.

EXAMPLE 68

A. 3-Amino-2,4-bis(methylthio)pyridine

(79% yield)
^1H NMR ($CDCl_3$): δ 2.45 (s, 3H); 2.60 (s, 3H); 4.14 (b, 2H); 6.88 (d, 1H); 7.90 (d, 1H).

EXAMPLE 69

B. 3-Amino-2,4-bis(ethylthio)pyridine

(86% yield)
^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H); 1.34 (t, 3H); 2.91 (q, 3H); 3.21 (q, 3H); 4.30 (b, 2H); 6.93 (d, 1H); 7.86 (d,1H).

EXAMPLE 70

C. 3-Amino-2,4-bis(ethyl)-6-methylpyridine

(86% yield)
^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H); 1.32 (t, 3H); 2.40 (s, 3H); 2.90 (q, 2H); 3.18 (q, 2H); 4.18 (b,2H); 6.79 (s, 1H).

EXAMPLE 71

(2S)-N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide

(S)-(-)-2-Hexylthiodecanoic, prepared according to Example IB, was coupled with 3-amino-2,4-bis-(methylthio)-6-methylpyridineby the procedure of Example 4B to yield the title compound in 55% yield; $[\alpha]_D^{RT}$ = -59° (CH_3OH). A sample recrystallized from petroleum ether had mp 81-83°C and $[\alpha]_D^{RT}$ = -66° (CH_3OH).

EXAMPLE 72

(2R)-N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 30.1% yield according to a procedure similar to that of Example 71. A sample recrystallized from petroleum ether had mp 80-82°C and $[\alpha]_D^{RT}$ = +61.7° (CH_3OH).

EXAMPLES 73

(2S)-N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 47.2% yield by the coupling of S-(-)-2-hexylthiodecanoic acid with 5-amino-4,6-bis(methylthio)-2-methylpyrimidine according to the procedure of Example 4A. A sample recrystallized from diethyl ether had mp 98-100°C and $[\alpha]_D^{RT}$ = -62° (CH_3OH).

EXAMPLE 74

(2R)-N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide

The title compound was prepared in 50.3% yield by a procedure similar to that of Example 73. A sample recrystallized from diethyl ether had mp 95-97.5°C and $[\alpha]_D^{RT}$ = +56.0° (CH_3OH).

EXAMPLE 75 (ILLUSTRATIVE EXAMPLE)

N-(6-methylthioquinolin-5-yl)-2-N,N-[(acyl)(hexyl)]aminodecanamide

To a stirred solution of N-(6-methylthioquinolin-5-yl)-2-hexylaminodecanamide (200 mg, 0.45 mmol) pyridine (10 ml) was added in one portion acetic anhydride (2.0 ml). After stirring at room temperature for 1 hour, the mixture was poured over 1.0 M H_3PO_4 (200 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined extracts were dried (Na_2SO_4), evaporated, and chromatographed using ethyl acetate as eluant to give the title compound (200 mg, 91% yield).

EXAMPLE 76

N-[4-dimethylamino-6-(cyano)(hexyl)aminopyrimidin-5-yl]-2-N,N-[(cyano)(hexyl)]aminodecanamide

To a stirred solution of N-[4-dimethylamino-6-hexylaminopyrimidin-5-yl)-2-hexylaminodecanamide (200 mg, 0.41 mmol), N-methyl morpholine (5 drops) in THF (5 ml) was added in one portion solid cyanobromide (95 mg, 220 mol%). After stirring at room temperature for 1 hour the mixture was chromatographed using 1:1/ethyl acetate:hexane as eluants to give the title compound (130 mg, 59% yield).

IR ($CHCl_3$) 3450, 3000-2800, 2200, 1740, 1650, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) δ 8.24 (s, 1H); 4.22 (m, 1H); 4.07 (m, 2H); 3.40 (m, 2H); 3.18 (m, 1H); 2.97 (s, 3H); 2.96 (s, 3H); 2.12 (m, 1H); 1.94 (m, 1H); 1.64 (m, 2H); 1.49 (m, 2H); 1.28 (m, 24H); 0.86 (m, 8H).

Mass spectrum m/e (relative intensity): M^+ 542 (100);

Anal. calc'd for $C_{30}H_{52}N_8O$: C, 66.6; H, 9.7; N, 20.7;

Found: C, 66.4; H, 9.8; N, 20.6.

EXAMPLE 77

N-[4,6-bis(dimethylamino)pyrimidin-5-yl]-cis-9-octadecenamide

5-Amino-4,6-bis(dimethylamino)pyrimidine (prepared by reacting commercially available 4,6-dichloro-5-nitro pyrimidine with excess dimethylamine followed by reduction of the nitro group according to the procedure of Jacobs et. al., J. Am. Chem. Soc., 42, 2278 (1920)) was coupled with oleoyl chloride using the procedure described in Example 4 to give the title compound.

^1H NMR ($CDCl_3$) δ 8.15 (s, 1H); 7.52 (s, 1H); 5.31 (m, 2H); 3.06 (s, 6H); 2.99 (s, 6H); 1.98 (m, 4H); 1.72 (m, 2H); 1.24 (m, 22H); 0.85 (m, 3H).

Mass spectrum m/e (relative intensity): M^+ 446 (100), 182 (47).

EXAMPLE 78

N-(4-dimethylamino-6-chloropyrimidin-5-yl)-cis-9-octadecenamide

5-Amino-4-(dimethyl)amino-6-chloropyrimidine (prepared by reacting commercially available 5-amino-4,6-dichloropyrimidine with excess dimethylamine) was coupled with oleoyl chloride according to the procedure described in Example 4 to give the title compound.

IR ($CHCl_3$) 3400, 3000-2800, 1700, 1570 cm^{-1}.

^1H NMR ($CDC1_3$) δ 8.23 (s, 1H); 6.82 (s, 1H); 5.34 (m, 2H); 3.15 (s, 6H); 2.40 (t, 2H, J = 7.6 Hz); 2.01 (m, 4H); 1.73 (m, 2H); 1.25 (m, 20H); 0.86 (m, 3H).

Mass spectrum m/e (relative intensity): M^+ 437 (100).

Anal. Calc'd for $C_{24}H_{41}N_4OC1$: C, 66.0; H, 9.5; N, 12.8.

Found: C, 65.7; H, 9.5; N, 12.9.

EXAMPLE 79

N-(4-dimethylamino-6-methylthiopyrimidin-5-yl)-cis-9-octadecenamide

5-Amino-4-dimethylamino-6-methylthiopyrimidine (prepared by reacting 5-amino-4-dimethylamino-6-chloropyrimidine with sodium thiomethoxide) was coupled with oleoyl chloride using the procedure described in Example 4 to give the title compound.

IR (KBr) 3220, 3000-2800, 1650, 1550 cm^{-1}.

^1H NMR ($CDCl_3$) δ 8.32 (s, 1H); 6.68 (s, 1H); 5.33 (m, 2H); 3.09 (s, 6H); 2.45 (s, 3H); 2.37 (t, 2H, J = 7.7 Hz); 2.00 (m, 4H); 1.72 (m, 2H); 1.25 (m, 20H); 0.86 (m, 3H).

Mass spectrum m/e (relative intensity): M^+ 449.4 (62), 185 (100). Anal. Calc'd for $C_{25}H_{44}N_4OS$: C, 66.9; H, 9.9; N, 12.5. Found: C, 67.3; H, 10.2; N, 12.4.

EXAMPLE 80

N-(4-dimethylamino-6-hexylaminopyrimidin-5-yl)-2-hexylaminodecanamide

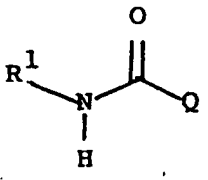
5-Amino-4-(dimethyl)amino-6-chloropyrimidine (prepared was coupled with 2-bromodecanoic acid using the procedure described in Example 75, followed by the addition of n-hexylamine to give the title compound.

IR ($CHC1_3$) 3280, 3000-2700, 1660, 1600 cm^{-1}. ^{1} H NMR ($CDC1_3$) δ 8.86 (s, 1H); 8.20 (s, 1H); 5.47 (t, 1H, J = 5.0 Hz); 3.40 (m, 2H); 3.18 (m, 1H); 2.88 (s, 6H); 2.66 (m, 2H); 1.85 (m, 1H); 1.44 (m, 31H); 0.86 (m, 8H).

Mass spectrum m/e (relative intensity): M^+ 491.5 (100). Anal. calc'd for $C_{28}H_{54}N_6O$: C, 68.5; H, 11.1; N, 17.1. Found: C, 68.8; H, 11.3; N, 17.5.

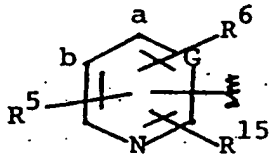
Claims

1. A compound of the formula



I

wherein Q is $-CR^2R^3R^4$;
R^1 is



XXVI

R^2, R^3 and R^4 may be the same or different, and
(a) are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, A, XR^{10}, phenyl-(C_1-C_7) alkyl, and (C_5-C_6) cycloalkyl-(C_1-C_6) alkyl, with the proviso that at least one of R^2, R^3 and R^4 must be A, and with the proviso that when R^1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, either at least one of R^2, R^3 and R^4 must be XR^{10}, or two of R^2, R^3 and R^4 must be A; or
(b) R^2 and R^3 together with the carbon to which they are attached form a cyclic or bicyclic system selected from the group consisting of (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, (C_6-C_{14}) bicycloalkyl, (C_6-C_{14}) bicycloalkenyl, and aryl-fused and heteroaryl-fused systems containing 8 to 15 carbon atoms, one ring of any of said aryl-fused and heteroaryl-fused systems being aromatic and the ring containing the carbon to which R^2 and R^3 are attached being non-aromatic, one of the carbons of said aromatic ring being optionally replaced by sulfur or oxygen, one or more carbons of said non-aromatic ring being optionally replaced by sulfur or oxygen, and one or more carbons of said aromatic ring being optionally replaced by nitrogen; one or two carbons of said cycloalkyl or bicycloalkyl groups being optionally replaced by sulfur or oxygen, and said cyclic or bicyclic system being optionally substituted with one to five substituents independently selected from the group consisting of phenyl, substituted phenyl, (C_1-C_6) alkyl and A, with the proviso that one and only one

of said substituents is A, and one and only one of said substituents is phenyl or substituted phenyl, said substituted phenyl being substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkylthio, halogen and trifluoromethyl; and R^4 is hydrogen, XR^{10} or A; with the proviso that when R^1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, R^2 and R^3, together with the carbon to which they are attached, do not form a (C_3-C_7) cycloalkyl ring containing only carbon atoms:

A is a hydrocarbon containing 4 to 16 carbons and 0, 1 or 2 double bonds:

X is O, S, SO, SO_2, NH, $NR^{23}CO$ or NSO_2R^{24}, wherein R^{23} is hydrogen or (C_1-C_6) alkyl and R^{24} is (C_1-C_6) alkyl, phenyl or (C_1-C_3) alkyl-phenyl:

R^5, R^6, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, (C_1-C_4)alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4)alkylthio, substituted phenylthio, heteroarylthio, heteroaryloxy, and $NR^{19}R^{20}$, wherein R^{19} and R^{20} are the same or different and are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, phenyl, substituted phenyl, (C_1-C_4) acyl, aroyl, and substituted aroyl, wherein said substituted phenyl and substituted aroyl groups are substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, halogen and trifluoromethyl, or R^{19} and R^{20}, together with the nitrogen to which they are attached, form a piperidine or morpholine ring; and wherein R^5, R^6, R^{15} and R^{16}, when attached to a bicyclic system, may be attached to either ring of such system, with the proviso that no more than 3 non-hydrogen substituents may be attached to any one ring of such system:

R^{10} is selected from the group consisting of (C_4-C_{12}) cycloalkyl, (C_4-C_{12}) straight or branched alkyl, (C_4-C_{12}) cycloalkyl-(C_1-C_6) alkyl, phenyl-(C_1-C_6) alkyl, (substituted phenyl)-(C_1-C_6) alkyl, (C_1-C_6) alkyl-phenyl, (C_1-C_6) alkyl-(substituted phenyl), substituted thiazoles, substituted benzothiazoles, and substituted pyridines; wherein the substituents on the substituted phenyl, substituted thiazoles, substituted benzothiazoles and substituted pyridines are selected from the group consisting of (C_1-C_4) alkoxy, (C_1-C_4) alkylthio, (C_1-C_6) alkyl, halo and trifluoromethyl:

G is selected from the group consisting of nitrogen and carbon with the proviso that when G is nitrogen, the group XXVI is attached to the nitrogen of formula I at the 4 or 5 position of the pyrimidine ring (designated by a and b):

or pharmaceutically acceptable salt of said compound.

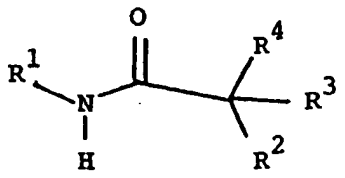
2. A compound according to claim 1 wherein R^1 is 4,6-bis(methylthio)-2-methylpyrimidin-5-yl and 2,4-bis-(methylthio)-6-pyridin-3-yl.

3. A compound according to claim 1, said compound being selected from the group consisting of:
(2S)-N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
(2S)-N-[2-methyl-4,6-bis(methylthio)pyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2-hexylthiodecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-hexylthiodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2,2-dimethyldocecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2,2-dimethyldodecanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-4,5-dimethyl-trans-2-heptylcyclohex-4-ene-carboxamide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-2-heptylnonanoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]pentadecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl-]pentadecanoic amide;
N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-(Z)-9-octadecenoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-(Z)-9-octadecenoic amide;
N-[4,6-bis(methylthio)-2-methylpyrimidin-5-yl]-trans-3-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide;
N-[4,6-bis(methylthio)pyrimidin-5-yl]-trans-3-nonyl-1,2,3,4-tetrahydro-2-naphthoic amide;

4. A pharmaceutical composition for inhibiting acyl coenzyme A: cholesterol acyltransferase, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol in a mammal, comprising an amount of a compound according to claim 1 that is effective in inhibiting acyl coenzyme A: cholesterol acyltransferase or intestinal absorption of cholesterol, or is effective in reversing or slowing the development of atherosclerosis or lowering the concentration of serum cholesterol, and a pharmaceutically acceptable carrier.

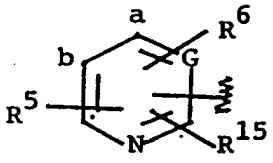
Claims for the following Contracting States : ES, GR

1. A process for making compound of the formula



I

wherein R^1 is



XXVI

R^2, R^3 and R^4 may be the same or different, and

(a) are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, A, XR^{10}, phenyl-(C_1-C_7) alkyl, and (C_5-C_6) cycloalkyl-(C_1-C_6) alkyl, with the proviso that at least one of R^2, R^3 and R^4 must be A, and with the proviso that when R^1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, either at least one of R^2, R^3 and R^4 must be XR^{10}, or two of R^2, R^3 and R^4 must be A; or

(b) R^2 and R^3 together with the carbon to which they are attached form a cyclic or bicyclic system selected from the group consisting of (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, (C_6-C_{14}) bicycloalkyl, (C_6-C_{14}) bicycloalkenyl, and aryl-fused and heteroaryl-fused systems containing 8 to 15 carbon atoms, one ring of said aryl-fused and heteroaryl-fused systems being aromatic and the ring containing the carbon to which R^2 and R^3 are attached being non-aromatic, one of the carbons of said aromatic ring being optionally replaced by sulfur or oxygen, one or more carbons of said non-aromatic ring being optionally replaced by sulfur or oxygen, and one or more carbons of said aromatic ring being optionally replaced by nitrogen; one or two carbons of said cycloalkyl or bicycloalkyl groups being optionally replaced by sulfur or oxygen, and said cyclic or bicyclic system being optionally substituted with one to five substituents independently selected from the group consisting of phenyl, substituted phenyl, (C_1-C_6) alkyl and A, with the proviso that one and only one of said substituents is A, and one and only one of said substituents is phenyl or substituted phenyl, said substituted phenyl being substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkylthio, halogen and trifluoromethyl; and R^4 is hydrogen, XR^{10} or A; with the proviso that when R^1 is a group of the formula XXVI wherein G is nitrogen and wherein neither R^5, R^6 nor R^{15} is $NR^{19}R^{20}$, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4) alkylthio, phenylthio or heteroalkylthio, R^2 and R^3, together with the carbon to which they are attached, do not form a (C_3-C_7) cycloalkyl ring containing only carbon atoms:

A is a hydrocarbon containing 4 to 16 carbons and 0, 1 or 2 double bonds:

X is O, S, SO, SO_2, NH, $NR^{23}CO$ or NSO_2R^{24}, wherein R^{23} is hydrogen or (C_1-C_6) alkyl and R^{24} is (C_1-C_6) alkyl, phenyl or (C_1-C_3) alkyl-phenyl:

R^5, R^6, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, (C_1-C_4)alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_6) alkylthio, (C_5-C_7) cycloalkylthio, phenyl (C_1-C_4)alkylthio, substituted phenylthio, heteroarylthio, heteroaryloxy, and $NR^{19}R^{20}$, wherein R^{19} and R^{20} are the same or different and are selected from the group consisting of hydrogen, (C_1-C_4) alkyl, phenyl, substituted phenyl, (C_1-C_4) acyl, aroyl, and substituted aroyl,

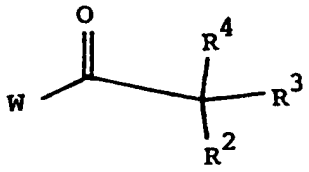
wherein said substituted phenyl and substituted aroyl groups are substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, halogen and trifluoromethyl or R^{19} and R^{20}, together with the nitrogen to which they are attached, form a piperidine or morpholine ring; and wherein R^5, R^6, R^{15} and R^{16}, when attached to a bicyclic system, may be attached to either ring of such system, with the proviso that no more than 3 non-hydrogen substituents may be attached to any one ring of such system:

R^{10} is selected from the group consisting of (C_4-C_{12}) cycloalkyl, (C_4-C_{12}) straight or branched alkyl, (C_4-C_{12}) cycloalkyl-(C_1-C_6) alkyl, phenyl-(C_1-C_6) alkyl, (substituted phenyl)-(C_1-C_6) alkyl, (C_1-C_6) alkyl-phenyl, (C_1-C_6) alkyl-(substituted phenyl), substituted thiazoles, substituted benzothiazoles, and substituted pyridines; wherein the substituents on the substituted phenyl, substituted thiazoles, substituted benzothiazoles and substituted pyridines are selected from the group consisting of (C_1-C_4) alkoxy, (C_1-C_4) alkylthio, (C_1-C_6) alkyl, halo and trifluoromethyl:

G is selected from the group consisting of nitrogen and carbon with the proviso that when G is nitrogen, the group XXVI is attached to the nitrogen of formula I at the 4 or 5 position of the pyrimidine ring (designated by a and b):

or a pharmaceutically acceptable salt thereof, comprising:

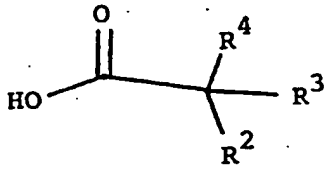
reacting a compound of the formula



IV

wherein W is chloro or bromo and R^2, R^3 and R^4 are defined as above, with an amine of the formula R^1NH_2, wherein R^1 is defined as above, and an acid scavenger.

2. A process according to claim 1, wherein said compound of the formula IV is obtained by reacting a compound of the formula



III

wherein R^2, R^3 and R^4 are defined as in claim 1, with a chlorinating or brominating agent.

3. A process according to claim 1 and claim 2, wherein said acid scavenger is selected from the group consisting of dimethylaminopyridine, pyridine and triethylamine, and said chlorinating or brominating agent is selected from the group consisting of oxalyl chloride, oxalyl bromide, thionyl chloride, thionyl bromide, phosphorus trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, phosphorous oxychloride and phosphorous oxybromide.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 94 20 0437

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X D	EP-A-0 283 742 (WARNER LAMBERT CO) * the whole document * & US-A-4 716 175 (WARNER LAMBERT CO)	1-4	C07D213/75 A61K31/44 C07D239/52 C07D239/58
X	FR-M-4 801 (J.R. GEIGY) * the whole document *	1,4	A61K31/505
D,X	EP-A-0 245 687 (WARNER LAMBERT CO) * the whole document *	1-4	
X	CHEMICAL ABSTRACTS, vol. 70, no. 17, 28 April 1969, Columbus, Ohio, US; abstract no. 77802r, J.R. GEIGY 'Alkanoic acid N-pyridylamides' page 332 ; * abstract * & FR-A-1 510 320 (J.R. GEIGY) 19 January 1968	1	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 May 1994	De Jong, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 94 20 0437

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 70, no. 15, 14 April 1969, Columbus, Ohio, US; abstract no. 68185q, J.R. GEIGY 'N-pyridyl aliphatic carboxylic amides' page 365 ; * abstract * & FR-A-1 510 319 (J.R. GEIGY) 19 January 1968 ---	1	
X	CHEMICAL ABSTRACTS. REGISTRY HANDBOOK - NUMBER SECTION. PRINTED ISSUES + MICROFILM COLUMBUS US * Compounds with RN=34808-93-0; 34808-94-1; 68134-77-0; 70933-06-1; 70933-07-2; 70933-08-3; 71669-56-2 ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
E	WO-A-91 04027 (PFIZER INC.) * the whole document * -----	1-4	

EP 94 20 0437

-C-

INCOMPLETE SEARCH

Claims searched completely: 2-4

Claim searched incompletely: 1

Claim 1 is so broad and so many novelty destroying compounds are disclosed in the prior art, that a complete search was not possible.

See Guidelines Part B, Chapter III, 3.6 and 3.7.